TESTS

pH (*2.2.3*): 5.0 to 8.0.

Dissolve 5.0 g with *carbon dioxide-free water R* and dilute to 25.0 mL with the same solvent.

Ester value (*2.5.2*): 10 to 75.

Ethylene oxide and dioxan (*2.4.25*): maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Impurity A. Liquid chromatography (*2.2.29*).

Test solution. Introduce 0.250 g of the substance to be examined into a 10 mL volumetric flask and add about 1 mL of *methanol R2*. Sonicate. Add about 8 mL of *water for chromatography R* and dilute to 10.0 mL with the same solvent. Filter.

Reference solution (a). Dissolve 5.0 mg of *vinyl acetate CRS* (impurity A) in *methanol R2* and dilute to 10.0 mL with the same solvent. Dilute 1.0 mL of this solution to 20.0 mL with *water for chromatography R*. Dilute 1.0 mL of this solution to 10.0 mL with *water for chromatography R*.

Reference solution (b). Dissolve 5 mg of *vinyl acetate R* (impurity A) and 5 mg of *1-vinylpyrrolidin-2-one R* in 10 mL of *methanol R2* and dilute to 50 mL with *water for chromatography R*. Dilute 1 mL of this solution to 20 mL with *water for chromatography R*.

A precolumn containing *octadecylsilyl silica gel for chromatography R* (5 µm) may be used if a matrix effect is observed.

Column:

– *size*: *l* = 0.25 m, Ø = 4.0 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 30 °C.

Mobile phase:

– *mobile phase A*: *acetonitrile R1, methanol R2, water for chromatography R* (5:5:90 *V/V/V*);
– *mobile phase B*: *methanol R2, acetonitrile R1, water for chromatography R* (5:45:50 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 40	100 → 85	0 → 15
40 - 42	85 → 0	15 → 100

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 10 µL.

Retention time: impurity A = about 19 min; 1-vinylpyrrolidin-2-one = about 25 min.

System suitability: reference solution (b):

– *resolution*: minimum 5.0 between the peaks due to impurity A and 1-vinylpyrrolidin-2-one.

Limit:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (100 ppm).

Impurity B. Liquid chromatography (*2.2.29*).

Test solution. Mix 0.200 g of the substance to be examined with *water for chromatography R* and dilute to 10.0 mL with the same solvent.

Reference solution. Dissolve 30 mg of *acetic acid R* (impurity B) and 30 mg of *citric acid R* in the mobile phase. Shake gently to dissolve and dilute to 100.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *0.005 M sulfuric acid.*

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 20 µL. After each injection, rinse the column with a mixture of equal volumes of *acetonitrile for chromatography R* and *0.005 M sulfuric acid*.

Retention time: impurity B = about 5 min; citric acid = about 7 min.

System suitability: reference solution:

– *resolution*: minimum 2.0 between the peaks due to citric acid and impurity B.

Limit:

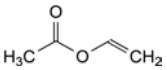
– *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (1.5 per cent).

Sulfated ash (*2.4.14*): maximum 3.0 per cent, determined on 5.0 g.

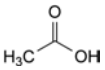
Loss on drying (*2.2.32*): maximum 5.0 per cent, determined on 1.000 g by drying *in vacuo* at 105 °C.

IMPURITIES

Specified impurities: *A, B.*



A. vinyl acetate,



B. acetic acid.

FUNCTIONALITY-RELATED CHARACTERISTICS

This section provides information on characteristics that are recognised as being relevant control parameters for one or more functions of the substance when used as an excipient (see chapter 5.15). This section is a non-mandatory part of the monograph and it is not necessary to verify the characteristics to demonstrate compliance. Control of these characteristics can however contribute to the quality of a medicinal product by improving the consistency of the manufacturing process and the performance of the medicinal product during use. Where control methods are cited, they are recognised as being suitable for the purpose, but other methods can also be used. Wherever results for a particular characteristic are reported, the control method must be indicated.

The following characteristics may be relevant for macrogol poly(vinyl alcohol) grafted copolymer used as film former in film-coated tablets.

Apparent viscosity (*2.2.10*): typically less than 250 mPa·s, determined on a 20 per cent (*m/m*) solution, using a rotating viscometer at 25 °C and rotation speed of 100 r/min.

01/2008:1444

MACROGOLS

Macrogola

DEFINITION

Mixtures of polymers with the general formula $H-(OCH_2-CH_2)_n-OH$ where *n* represents the average number of oxyethylene groups. The type of macrogol is defined by a number that indicates the average relative molecular mass. A suitable stabiliser may be added.

CHARACTERS

Type of macrogol	Appearance	Solubility
300 400 600	clear, viscous, colourless or almost colourless hygroscopic liquid	miscible with water, very soluble in acetone, in alcohol, and in methylene chloride, practically insoluble in fatty oils and in mineral oils
1000	white or almost white, hygroscopic solid with a waxy or paraffin-like appearance	very soluble in water, freely soluble in alcohol and in methylene chloride, practically insoluble in fatty oils and in mineral oils
1500	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, freely soluble in alcohol, practically insoluble in fatty oils and in mineral oils
3000 3350	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, very slightly soluble in alcohol, practically insoluble in fatty oils and in mineral oils
4000 6000 8000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water and in methylene chloride, practically insoluble in alcohol and in fatty oils and in mineral oils
20 000 35 000	white or almost white solid with a waxy or paraffin-like appearance	very soluble in water, soluble in methylene chloride, practically insoluble in alcohol and in fatty oils and in mineral oils

IDENTIFICATION

A. It complies with the test for viscosity (see Tests).

B. To 1 g in a test-tube add 0.5 mL of *sulfuric acid R*, close the test-tube with a stopper fitted with a bent delivery tube and heat until white fumes are evolved. Collect the fumes via the delivery tube into 1 mL of *mercuric chloride solution R*. An abundant white, crystalline precipitate is formed.

C. To 0.1 g add 0.1 g of *potassium thiocyanate R* and 0.1 g of *cobalt nitrate R* and mix thoroughly with a glass rod. Add 5 mL of *methylene chloride R* and shake. The liquid phase becomes blue.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution BY_6 (*2.2.2, Method II*).

Dissolve 12.5 g in *water R* and dilute to 50 mL with the same solvent.

Table 1444.-1

Type of macrogol	Kinematic viscosity ($mm^2 \cdot s^{-1}$)	Dynamic viscosity (mPa·s)	Density* (g/mL)
300	71 - 94	80 - 105	1.120
400	94 - 116	105 - 130	1.120
600	13.9 - 18.5	15 - 20	1.080
1000	20.4 - 27.7	22 - 30	1.080
1500	31 - 46	34 - 50	1.080
3000	69 - 93	75 - 100	1.080
3350	76 - 110	83 - 120	1.080
4000	102 - 158	110 - 170	1.080
6000	185 - 250	200 - 270	1.080
8000	240 - 472	260 - 510	1.080
20 000	2500 - 3200	2700 - 3500	1.080
35 000	10 000 - 13 000	11 000 - 14 000	1.080

*Density of the substance for macrogols 300 and 400. Density of the 50 per cent *m/m* solution for the other macrogols.

Acidity or alkalinity. Dissolve 5.0 g in 50 mL of *carbon dioxide-free water R* and add 0.15 mL of *bromothymol blue solution R1*. The solution is yellow or green. Not more than 0.1 mL of *0.1 M sodium hydroxide* is required to change the colour of the indicator to blue.

Viscosity (*2.2.9*). The viscosity is calculated using a density given in Table 1444.-1.

For macrogols having a relative molecular mass greater than 400, determine the viscosity on a 50 per cent *m/m* solution of the substance to be examined.

Freezing point (*2.2.18*). See Table 1444.-2.

Table 1444.-2

Type of macrogol	Freezing point (°C)
600	15 - 25
1000	35 - 40
1500	42 - 48
3000	50 - 56
3350	53 - 57
4000	53 - 59
6000	55 - 61
8000	55 - 62
20 000	minimum 57
35 000	minimum 57

Hydroxyl value. Introduce *m* g (see Table 1444.-3) into a dry conical flask fitted with a reflux condenser. Add 25.0 mL of *phthalic anhydride solution R*, swirl to dissolve and boil under a reflux condenser on a hot plate for 60 min. Allow to cool. Rinse the condenser first with 25 mL of *pyridine R* and then with 25 mL of *water R*, add 1.5 mL of *phenolphthalein solution R* and titrate with *1 M sodium hydroxide* until a faint pink colour is obtained (n_1 mL). Carry out a blank test (n_2 mL). Calculate the hydroxyl value using the expression:

$$\frac{56.1 \times (n_2 - n_1)}{m}$$

Table 1444.-3

Type of macrogol	Hydroxyl value	*m* (g)
300	340 - 394	1.5
400	264 - 300	1.9
600	178 - 197	3.5
1000	107 - 118	5.0
1500	70 - 80	7.0
3000	34 - 42	12.0
3350	30 - 38	12.0
4000	25 - 32	14.0
6000	16 - 22	18.0
8000	12 - 16	24.0
20 000	-	-
35 000	-	-

For macrogols having a relative molecular mass greater than 1000, if the water content is more than 0.5 per cent, dry a sample of suitable mass at 100-105 °C for 2 h and carry out the determination of the hydroxyl value on the dried sample.

Monographs M

Reducing substances. Dissolve 1 g in 1 mL of a 10 g/L solution of *resorcinol R* and warm gently if necessary. Add 2 mL of *hydrochloric acid R*. After 5 min the solution is not more intensely coloured than reference solution R_3 (*2.2.2, Method I*).

Formaldehyde: maximum 30 ppm.

Test solution. To 1.00 g add 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Allow to stand for 15 min and complete slowly to 10 mL with *water R*.

Reference solution. Dilute 0.860 g of *formaldehyde solution R* to 100 mL with *water R*. Dilute 1.0 mL of this solution to 100 mL with *water R*. In a 10 mL flask, mix 1.00 mL of this solution with 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Allow to stand for 15 min and complete slowly to 10 mL with *water R*.

Blank solution. In a 10 mL flask mix 1.00 mL of *water R* with 0.25 mL of *chromotropic acid, sodium salt solution R*, cool in iced water and add 5.0 mL of *sulfuric acid R*. Complete slowly to 10 mL with *water R*.

Determine the absorbance (*2.2.25*) of the test solution at 567 nm, against the blank solution. It is not higher than that of the reference solution.

If the use of macrogols with a higher content of formaldehyde may have adverse effects, the competent authority may impose a limit of not more than 15 ppm.

Ethylene glycol and diethylene glycol: *carry out this test only if the macrogol has a relative molecular mass below 1000.*

Gas chromatography (*2.2.28*).

Test solution. Dissolve 5.00 g of the substance to be examined in *acetone R* and dilute to 100.0 mL with the same solvent.

Reference solution. Dissolve 0.10 g of *ethylene glycol R* and 0.50 g of *diethylene glycol R* in *acetone R* and dilute to 100.0 mL with the same solvent. Dilute 1.0 mL of this solution to 10.0 mL with *acetone R*.

Column:

- *material*: glass,
- *size*: *l* = 1.8 m, Ø = 2 mm,
- *stationary phase*: *silanised diatomaceous earth for gas chromatography R*, impregnated with 5 per cent *m/m* of *macrogol 20 000 R*,

Carrier gas: *nitrogen for chromatography R*.

Flow rate: 30 mL/min.

Temperature:

- *column*: if necessary, precondition the column by heating at 200 °C for about 15 h; adjust the initial temperature of the column to obtain a retention time of 14-16 min for diethylene glycol; raise the temperature of the column by about 30 °C at a rate of 2 °C/min but without exceeding 170 °C;
- *injection port and detector*: 250 °C.

Detection: flame ionisation.

Injection: 2 µL.

Carry out 5 replicate injections to check the repeatability of the response.

Limit: maximum 0.4 per cent, calculated as the sum of the contents of ethylene glycol and diethylene glycol.

Ethylene oxide and dioxan (*2.4.25*): maximum 1 ppm of ethylene oxide and 10 ppm of dioxan.

Heavy metals (*2.4.8*): maximum 20 ppm.

Dissolve 2.0 g in *water R* and dilute to 20 mL with the same solvent. 12 mL of the solution complies with limit test A. Prepare the standard using *lead standard solution (2 ppm Pb) R*.

Water (*2.5.12*): maximum 2.0 per cent for macrogol with a relative molecular mass not greater than 1000 and maximum 1.0 per cent for macrogol with a relative molecular mass greater than 1000, determined on 2.00 g.

Sulfated ash (*2.4.14*): maximum 0.2 per cent, determined on 1.0 g.

STORAGE

In an airtight container.

LABELLING

The label states:

- the type of macrogol,
- the content of formaldehyde.

01/2008:2396
corrected 7.0

MACROGOL 40 SORBITOL HEPTAOLEATE

Macrogol 40 sorbitoli heptaoleas

DEFINITION

Mixture of esters of fatty acids, mainly *Oleic acid (0799)*, and sorbitol ethoxylated with approximately 40 moles of ethylene oxide for each mole of sorbitol. 7 moles of oleic acid are used for each mole of sorbitol. It also contains macrogol fatty acid esters.

CHARACTERS

Appearance: clear or slightly opalescent, yellowish, viscous, hygroscopic liquid.

Solubility: dispersible in water, soluble in isopropyl myristate, in isopropyl palmitate, in mineral oils and in vegetable fatty oils.

Relative density: about 1.0.

Viscosity (*2.2.9*): about 175 mPa·s at 25 °C.

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *macrogol 40 sorbitol heptaoleate CRS*.

B. Hydroxyl value (see Tests).

C. Saponification value (see Tests).

D. Composition of fatty acids (see Tests).

TESTS

Acid value (*2.5.1*): maximum 12.0, determined on 3.0 g.

Hydroxyl value (*2.5.3, Method A*): 22 to 55.

Peroxide value: maximum 10.0.

Introduce 10.0 g into a 100 mL beaker and dissolve with 20 mL of *glacial acetic acid R*. Add 1 mL of *saturated potassium iodide solution R*, mix and allow to stand for 1 min. Add 50 mL of *carbon dioxide-free water R* and a magnetic stirring bar. Titrate with *0.01 M sodium thiosulfate*, determining the end-point potentiometrically (*2.2.20*). Carry out a blank titration.

Determine the peroxide value using the following expression:

$$\frac{(n_1 - n_2) \times M \times 1000}{m}$$

n_1 = volume of *0.01 M sodium thiosulfate* required for the titration of the substance to be examined, in millilitres;

n_2 = volume of *0.01 M sodium thiosulfate* required for the blank titration, in millilitres;

M = molarity of the sodium thiosulfate solution;

m = mass of the substance to be examined, in grams.

Saponification value (*2.5.6*): 90 to 110, determined on 4.0 g.

Use 30.0 mL of *0.5 M alcoholic potassium hydroxide*, heat under reflux for 60 min and add 50 mL of *anhydrous ethanol R* before carrying out the titration.